REMARKS

Claims 1, 2, 4, 6-11, 21, and 26-28 are pending in the instant application. Claims 1, 2, 4, 6-11, 21, and 26-28 have been rejected. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Rejection of Claims Under 35 U.S.C. §103

Claims 1, 2, 4, 6-11, 21, and 26-28 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Gjerde et al. (U.S. Patent Application No. 2003/0165941) in view of Bloch (U.S. Patent No. 5,866,429). It is suggested that Gjerde et al. teach separation of polynucleotides by Matched Ion Polynucleotide Chromatography (MIPC) in accordance with the claimed methods; however, this reference does not teach that the column has an inner diameter of greater than 5.0 mm. The Examiner suggests that Petrovic & Jankovic and Bloch teach that the internal diameter of the columns can be greater than 5 mm. It is suggested that Petrovic & Jankovic teach that the column in simple ion exchange methods for RNA separation can be between 4-6 mm and Bloch teaches that the column is the most important component, wherein the column can be no greater than 10 mm, *i.e.*, naturally encompassing diameters greater than 5 mm. The Examiner suggests that it would have been obvious to one of ordinary skill in the art at the time of filing to include the internal diameter sizes taught by Bloch and Petrovic & Jankovic with the method of separation of RNA molecules taught by Gjerde et al. because Gjerde et al. teach that it is within the ordinary skill of the art to separate RNA using non-polar separation medium in which a

mobile phase is passed through to elute RNA and because Bloch and Petrovic & Jankovic teach that it is within ordinary skill in the art to use columns with internal diameters of greater than 5 mm. It is suggested that one would have been motivated to do so in order to receive the expected benefit of preferred components of RNA separation. Applicants respectfully traverse this rejection.

MPEP § 2141 states that when applying 35 U.S.C. 103, the following tenets of patent law must be adhered to: (A) The claimed invention must be considered as a whole; (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (D) Reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

As a whole, the claimed invention is drawn to the use of columns comprising a non-polar separation medium with an inner diameter of greater than 5 mm for optimal purification and stabilization of RNA molecules (see page 1, lines 12-14, and page 28, lines 7-18).

As a whole, Gjerde et al. teach and exemplify the separation of double-stranded DNA utilizing a stationary separation medium having non-polar surfaces. This reference does not teach the separation of an RNA molecule from an RNA degrading agent using a column having an inner diameter of greater than about 5 mm.

Petrovic & Jankovic teach the quantification and analysis of RNA-derived *mononucleotides* using analytical ion exchange columns with inner diameters of 4-6 mm.

As a whole, Bloch teaches the advantages of using analytical anion exchange chromatography in the separation of double-stranded DNA, because reverse-phase separation is not optimal for analyzing DNA (column 5, lines 27-40). Further, Bloch specifically states that "[f]or analytical separations, column internal diameter will not exceed 10 mm and *preferably will not exceed 5 mm*" (column 17, lines 21-23).

Applicants respectfully believe that the Examiner has used impermissible hindsight in combining the cited references as there is simply no suggestion, motivation, or desirability to make such a combination in the references themselves or in the knowledge generally available to one of ordinary skill in the art, particularly with the cited references in hand.

At the outset, Applicants respectfully wish to point out to the Examiner that the skilled artisan would find little motivation or desirability to combine the teachings of Petrovic & Jankovic with the teachings of any of the other cited references to arrive at the instant invention because Petrovic & Jankovic is drawn to the analysis of degraded RNA using ion exchange chromatography. The whole focus of the instant application is the *purification and stabilization of intact RNA molecules* by reverse-phase chromatography.

Likewise, Bloch fails to suggest the desirability and thus the obviousness of making the combination because the separation methodology disclosed in Bloch is based on anion exchange chromatography, wherein the instant specification teaches reverse-phase chromatography. A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. W.L. Gore &

Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). MPEP 2142.02. In this regard, Bloch teaches that reverse-phase separation is not optimal for analyzing DNA and provides general guidelines which indicate that smaller column inner diameters, *i.e.*, not exceeding 5 mm, are preferred. Accordingly, there would be little motivation for one of skill in the art to modify the teachings of Bloch to use the non-polar surfaces of Gjerde et al. in a column having an inner diameter greater than 5 mm, because neither Bloch nor Gjerde et al. suggest the desirability of such a combination.

Thus, the suggestion or motivation to modify or to combine the referenced teachings is lacking and therefore the claimed invention is not obvious in accord with the requirement set forth in MPEP 2142. It is therefore respectfully requested that this rejection be withdrawn.

Claims 7-10, 26 and 28 have also been rejected under 35 U.S.C. 103(a) as being unpatentable over Oefner (U.S. Patent No. 6,453,244) in view of Bloch. It is suggested that Oefner teaches separation of polynucleotides MIPC in accordance with the claimed methods; however, this reference does not teach that the column has an inner diameter of greater than 5.0 mm. The Examiner suggests that Petrovic & Jankovic and Bloch teach that the internal diameter of the columns can be greater than 5 mm. It is suggested that Petrovic & Jankovic teach that the column in simple ion exchange methods for RNA separation can be between 4-6 mm and Bloch teaches that the column is the most important component, wherein the column can be no greater than 10 mm, *i.e.*, naturally encompassing diameters greater than 5 mm. The Examiner

suggests that it would have been obvious to one of ordinary skill in the art at the time of filing to include the internal diameter sizes taught by Bloch and Petrovic & Jankovic with the method of separation of RNA molecules taught by Oefner because Oefner teaches that it is within the ordinary skill of the art to separate RNA using non-polar separation medium in which a mobile phase is passed through to elute RNA and because Bloch and Petrovic & Jankovic teach that it is within ordinary skill in the art to use columns with internal diameters of greater than 5 mm. It is suggested that one would have been motivated to do so in order to receive the expected benefit of preferred components of RNA separation. Applicants respectfully traverse this rejection.

Oefner teaches the analysis of nucleic acids by denaturing a sample and applying the denatured sample to a stationary reverse-phase support. Oefner does not teach the separation of an RNA degrading agent from an RNA molecule, thereby stabilizing the RNA molecule against degradation. Nor does Oefner appreciate the use of using a column having an inner diameter of greater than about 5 mm.

As indicated above, Bloch teaches anion exchange using a column diameter not exceeding 5 mm because reverse-phase is not suitable for DNA analysis, and Petrovic & Jankovic teach analysis of degraded RNA using ion exchange chromatography. The teachings of Bloch and Petrovic & Jankovic simply provide no suggestion, motivation, or desirability to modify the teachings therein to apply a stationary reverse-phase support, *e.g.*, as disclosed by Oefner. Likewise, Oefner provides no suggestion, motivation, or desirability to modify the teachings therein to employ a column diameter of greater than 5 mm. Because the cited references fail

to suggest the desirability and thus the obviousness of making the combination, the cited references fail to make the instant invention obvious. It is therefore respectfully requested that this rejection be withdrawn.

Claims 1, 2, 4, 6 and 21 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Oefner, in view of Bloch, further in view of Petro et al. (U.S. Patent No. 6,260,407). Claims 11 and 27 also stand rejected under 35 U.S.C. 103(a) as being unpatentable over Oefner, in view of Bloch, further in view of Petro et al., further in view of Sheridan and Sheridan ((1989) *Scientist* 3(4)23). Applicants respectfully traverse these rejections.

As indicated *supra*, Oefner fails to teach or suggest optimal conditions (*i.e.*, column inner diameters of greater than about 5 mm) for separation of an RNA molecule from an RNA degrading agent, thereby stabilizing the RNA molecule against degradation. Further, there would be little motivation to modify the teachings of Oefner based upon the teachings of Bloch, because Bloch teaches anion exchange using a column diameter preferably not exceeding 5 mm. Moreover, Petro and Sheridan & Sheridan also fail to appreciate a column inner diameter greater than 5 mm for optimal separation of RNA. Accordingly, because the cited references fail to provide some suggestion or motivation to modify the reference teachings or to combine the reference teachings, they fail to make the instant invention obvious. It is therefore respectfully requested that these rejections be withdrawn.

II. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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Date: **June 13, 2005**

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